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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FLUOMETURON

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 10105
and
National Toxicology Program
Research Triangle Park
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FOREWORD

This report presents the results of the bioassay of fluometuron conducted for the Carcinogenesis Testing Program, National Cancer Institute (NCI), National Toxicology Program (NTP). This is one of a series of experiments designed to determine whether selected environmental chemicals have the capacity to produce cancer in animals. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that a test chemical is carcinogenic for animals under the conditions of the test and indicates that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

CONTRIBUTORS

This bioassay of fluometuron was conducted by Gulf South Research Institute (GSRI), New Iberia, Louisiana, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design for this bioassay is based on guidelines that have been established for carcinogen bioassays in small animals (NCI, 1976). The doses for the chronic studies were selected by Drs. E. E. Storrs (1), O. G. Fitzhugh (2), the late C. N. Barron (3), J. F. Robens (3,4), and C. Cueto (5,6). The principal investigator was Mr. R. J. Wheeler (1). Histologic examination of animal tissues was performed by Dr. B. Buratto (1).

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (7), and statistical analyses were performed by Dr. J. R. Joiner (3) and Ms. S. Vatsan (3) using methods selected for the bioassay program by Dr. J. J. Gart (8). Chemicals were analyzed at GSRI by Mr. Wheeler and dosed feed mixtures by Mr. S. M. Billedeau. The results of these analyses were reviewed by Dr. C. W. Jameson (3,9). The chemical was reanalyzed at Midwest Research Institute (10) upon completion of the bioassay.

This report was prepared at Tracor Jitco (3) under the direction of NCI. Those responsible for the report were Dr. C. R. Angel, Director of the

Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. R. L. Schueler, pathologist; Dr. A. C. Jacobs, bioscience writer; and Dr. W.D. Theriault and Ms. M.W. Glasser, technical editors.

The following scientists at NCI were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr. (5,6), Dr. Michael P. Dieter, Dr. J. Fielding Douglas, Dr. Charles K. Grieshaber, Dr. Richard A. Griesemer, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Y. Jack Lee, Dr. Harry Mahar, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Marcelina B. Powers, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of the phenylurea herbicide fluometuron for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats of each sex were fed diets containing 125 or 250 ppm of fluometuron for 103 weeks, and groups of 50 mice of each sex were fed diets containing 500 or 1,000 ppm of fluometuron for 103 weeks. Matched controls consisted of groups of 50 untreated rats and 25 untreated mice of each sex. All surviving animals were killed at 103 to 105 weeks.

Splenomegaly observed in rats in the subchronic studies influenced selection of doses for the chronic study; however, no splenic effects were observed in the chronic study.

Mean body weights of the dosed groups of male and female rats and mice were essentially the same as those of the corresponding control groups. Survival of dosed groups of rats and mice was similar to that of the corresponding control groups. Similarities between mean body weights and survival between dosed and control animals in the chronic study suggest that these animals could have tolerated higher doses.

The only possible carcinogenic effects from compound administration were in male mice. Incidences of hepatocellular carcinomas or adenomas in male mice were dose related, and the incidence in the high-dose group was marginally higher than that in the corresponding matched controls or pooled controls from concurrent studies.

Under the conditions of this bioassay, fluometuron was not carcinogenic for F344 rats or for female B6C3F1 mice. Equivocal results were obtained for male B6C3F1 mice which may have had an increased incidence of hepatocellular tumors. Because of the equivocal findings and because both rats and mice may have been able to tolerate higher doses, it is concluded that additional testing of fluometuron for carcinogenicity is warranted.

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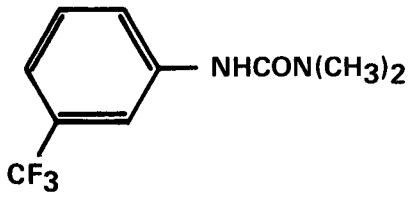
I. INTRODUCTION

Fluometuron, 1,1-dimethyl-3-(alpha, alpha, alpha-trifluoro-m-tolyl) urea (CAS 2164-17-2; NCI C08695) is a phenylurea herbicide used in agriculture to control broad-leaved and grass weeds in cotton and sugarcane fields (EPA, 1970; Meister, 1977). The area of heaviest use is the Mississippi delta (Weed Society of America, 1979). Applications of low concentrations selectively kill weeds (Ciba-Geigy, 1963).



FLUOMETURON

Commercial preparations of fluometuron are wettable powders containing either 80% active ingredient or 13% active ingredient in combination with 27% monosodium acid methanearsonate (Ciba-Geigy, 1972). Before application, these products are mixed with water to form a suspension which is then sprayed either on the ground for preemergent weed control or directly on standing weeds. Absorption occurs primarily through the roots, although there is some foliar uptake (Martin and Worthing, 1977; Spencer, 1973).

Fluometuron has a half-life of 60 to 75 days (Martin and Worthing, 1977) and is active for 2 to 5 months after the initial application (Melnikov, 1971). This herbicide is degraded to m-(trifluoromethyl)-aniline in plants and animals (Spencer, 1973).

Fluometuron has been marketed in the United States since 1960. The amounts used in agriculture were 3.3 million pounds in 1971 (U. S. Dept. of Agriculture, 1974) and 5.3 million pounds in 1976 (U. S. Dept. of Agriculture, 1978).

The reported acute oral LD_{50} of fluometuron is 8,910 mg/kg body weight for male rats (unspecified strain) and 7,880 mg/kg body weight for female rats (unspecified strain) (Ciba-Geigy, 1972). For male mice, the oral LD_{50} was reported to be 900 mg/kg and for females 2,320 mg/kg (Ciba-Geigy, 1972). Signs of depression, hyperpnea, gasping, lacrimation,

peripheral vasoconstriction, and coma were observed in animals given lethal doses (Ciba-Geigy, 1972).

Seiler (1978) found that fluometuron inhibited testicular DNA synthesis and was also weakly mutagenic in the Salmonella typhimurium test.

Demethylation appears to play an important role in the metabolism of 1,1-dimethyl-3-arylurea herbicides (Muecke et al., 1976). Using human embryonic lung-cell cultures, Lin et al. (1976) identified three products of the oxidative demethylation of fluometuron. Moreover, nitrosation of 1-methyl-3-phenylurea (MPU), the demethylated product of fenuron (1,1-dimethyl-3-pheylurea) -- a close structural analog of fluometuron -- was shown to occur in vitro in the presence of MPU, sodium nitrite, and an acid environment (Warzok et al., 1978). MPU was not carcinogenic when administered by gavage to strain E rats; however, when administered with sodium nitrite, the compound was strongly carcinogenic, producing carcinomas of the forestomach (15/25) and tumors of the liver (6/25) (Warzok et al., 1978).

Due to the potential exposure of agricultural workers during application, the persistence of the chemical in the soil for 2 to 5 months, and the apparent lack of long-term testing data in laboratory animals, fluometuron was selected for testing by the NCI Carcinogenesis Testing Program.

II. MATERIALS AND METHODS

A. Chemical

Fluometuron was obtained in a single batch (Lot No. FL-741086) from Ciba-Geigy Corporation, Agricultural Division, Ardsley, New York. Analysis of this batch at Gulf South Research Institute (elemental analysis, melting point, thin-layer and gas-liquid chromatography, and infrared, ultraviolet, and nuclear magnetic resonance spectrometry) confirmed the identity of the white crystalline test chemical and indicated a purity greater than 99% (Appendix E). No attempt was made to identify or quantitate impurities. The chemical was stored in the original container at approximately 25°C. Results from infrared and nuclear magnetic resonance spectrometry and from vapor-phase and high-pressure liquid chromatography of this batch of fluometuron by Midwest Research Institute after completion of the bioassay indicated that no decomposition occurred under these storage conditions.

B. Dietary Preparation

All diets were formulated using Wayne® Lab-Blox Meal (Allied Mills, Chicago, Ill.) to which was added the required amount of fluometuron for each dietary concentration. The test compound was first dissolved in a small amount of acetone (Mallinckrodt Chemicals, St. Louis, Mo.) which was then added to the feed. Corn oil (Lou Ana®, Opelousas Refinery, Opelousas, La.) was also added to the feed, primarily as a dust suppressant. Final diets, including those for the control groups of animals, contained corn oil equal to 2% of the final weight of feed. The diets were mixed mechanically for not less than 25 minutes to assure homogeneity and to allow for evaporation of the acetone. Formulated diets were stored at room temperature until used, but not longer than 1 week.

Measurement of fluometuron concentration in diets containing 500 and 1,000 ppm indicated the test chemical was stable in these proportions at ambient temperature for 7 days.

As a quality control check on the accuracy of preparation of the diets, the concentration of fluometuron was determined analytically in randomly selected batches of formulated diets at 8-week intervals during the chronic study. At each dietary concentration, the mean of the analytical concentration was within 2% of theoretical, and the coefficient of variation was not greater than 6.7% (Appendix F).

C. Animals

Male and female F344 (Fischer) rats and B6C3F1 hybrid mice, obtained from the NCI Frederick Cancer Research Center (Frederick, Md.), were housed within the test facility for 16 days and assigned to dosed or control groups. In the chronic study, the rats and the mice were approximately 7 weeks old at the time of the test initiation.

D. Animal Maintenance

Rats were housed individually in hanging galvanized steel mesh cages (Hoeltge, Cincinnati, Ohio). Mice were housed either five per cage (females) or two or three per cage (males) in polypropylene cages (Lab Products, Inc., Garfield, N.J.) covered with polyester filter bonnets (Lab Products, Inc.). Mouse cages were washed twice each week, and rat cages once every 2 weeks. Cages and racks were washed in an industrial washer (Industrial Washing Machine Corp., Matawan, N.J.) at 82°C with Acclaim® detergent (Economics Laboratory, Inc., St. Paul, Minn.) and then rinsed. Absorbent Kimpak® cage liners (Kimberly Clark Corp., Neenah, Wis.) were placed under the rat cages and were changed three times per week. Absorb-dri® hardwood chip bedding (Lab Products, Inc.) was used in the mouse cages and was changed twice per week. Feed jars, water bottles, sipper tubes, and stoppers were washed twice weekly in a Vulcan Autosan washer (Louisville, Ky.) at 82°C, using Acclaim® detergent, and then rinsed.

Fluometuron was the only compound on test in each room. Rats and mice were housed in separate rooms. Cage racks for each species were rotated to a new position in the room once a week; at the same time, each cage was moved to a different row within the same column of a rack. Control and

dosed rats were housed on the same rack, whereas cages for control and dosed mice were placed on separate racks in the same room.

The animal rooms were maintained at 22° to 24°C, and the relative humidity ranged from 40% to 70%. Air vents were fitted with permanent air maze filters (Air Maze Incom International, Cleveland, Ohio), and a single-pass-through air handling system provided 10 to 12 changes of room air per hour. Fluorescent lighting provided illumination 10 hours per day. Fresh food was supplied twice per week, and feed that had not been consumed from the previous feeding was discarded. Water obtained from the city water system was available ad libitum.

E. Subchronic Studies

Subchronic feeding studies were conducted to determine the two concentrations (referred to in this report as "low" and "high" doses) to be used in the chronic studies. Fluometuron was administered in the diet for 90 days at doses of 0, 250, 500, 1,000, 2,000, 4,000, 8,000, or 16,000 ppm to groups consisting of 10 males and 10 females of each species (Tables 1 and 2).

Animals were observed daily for toxic effects and behavior, and body weights and food consumption were recorded weekly. At the end of the 90-day period, the animals were weighed, anesthetized with chloroform, exsanguinated, and necropsied.

Deaths occurred among male rats fed diets containing 8,000 and 16,000 ppm and females receiving 16,000 ppm. Lower weight gain relative to the controls was seen in males and females at the three highest doses (4,000, 8,000, and 16,000 ppm).

Varying degrees of splenomegaly not observed in controls were seen in both male and female rats fed fluometuron at levels of 2,000 ppm or more. Microscopic examination was performed on spleen tissues from male rats receiving 0, 4,000, 8,000, or 16,000 ppm and females receiving 8,000 ppm. Pathologic changes, which were dose related, included mild to severe hyperemia of the red pulp, with a corresponding degree of atrophy of the Malpighian corpuscles and depletion of the lymphocytic elements. Most of the red blood cells appeared intact, and the amount of hemosiderin pigment was normal.

Table 1. Doses, Survival, and Mean Body Weights of Rats Fed Fluometuron in the First 90-Day Subchronic Study

Dose (ppm)	Survival (a)	Mean Body Weights (grams) Initial	Final	Gain	Weight Change Relative to Controls (b) (Percent)
MALES					
0	10/10	98	295	197	
250	10/10	95	297	202	+3
500	10/10	93	290	197	0
1,000	10/10	99	289	190	-4
2,000	10/10	107	299	192	-3
4,000	10/10	108	280	172	-13
8,000	9/10	98	242	144	-27
16,000	6/10	90	190	100	-49
FEMALES					
0	10/10	87	182	95	
250	10/10	84	187	103	+8
500	10/10	89	189	100	+5
1,000	10/10	77	177	100	+5
2,000	10/10	84	177	93	-2
4,000	10/10	83	167	84	-12
8,000	10/10	79	162	83	-13
16,000	3/10	76	143	67	-29

(a) Number surviving/number per group.

(b) Weight Change Relative to Controls =

$$\frac{\text{Weight Gain (Dosed Group)} - \text{Weight Gain (Control Group)}}{\text{Weight Gain (Control Group)}} \times 100$$

Table 2. Doses, Survival, and Mean Body Weights of Mice Fed Fluometuron in the 90-Day Subchronic Study

Dose (ppm)	Survival (a)	Mean Body Weights (grams) Initial	Final	Gain	Weight Change Relative to Controls (b) (Percent)
MALES					
0	10/10	20.9	27.8	6.9	
250	10/10	20.0	28.2	8.2	+19
500	10/10	20.4	27.5	7.1	+3
1,000	10/10	20.4	28.8	8.4	+22
2,000	10/10	19.5	28.0	8.5	+23
4,000	10/10	21.6	27.5	5.9	-15
8,000	10/10	21.1	27.2	6.1	-12
16,000	10/10	20.7	26.1	5.4	-22
FEMALES					
0	10/10	18.2	23.4	5.2	
250	10/10	18.0	23.8	5.8	+12
500	9/10	17.6	26.3	8.7	+67
1,000	10/10	17.3	22.9	5.6	+8
2,000	10/10	17.7	23.5	5.8	+12
4,000	10/10	19.0	22.7	3.7	-29
8,000	10/10	17.8	21.8	4.0	-22
16,000	10/10	17.8	20.7	2.9	-44

(a) Number surviving/number per group.

(b) Weight Change Relative to Controls =

$$\frac{\text{Weight Gain (Dosed Group)} - \text{Weight Gain (Control Group)}}{\text{Weight Gain (Control Group)}} \times 100$$

A second 90-day subchronic study, described in Table 3, was undertaken to investigate in-depth the effects of feed containing 0 to 4,000 ppm fluometuron on the spleens of rats. Factors such as behavior and food consumption in the dosed groups were similar to those in the controls. Mean weight gain of all dosed males was less than that in the controls, but in the females only the mean weight gain of the group fed 4,000 ppm was depressed more than 10 percent compared with control values.

Mean weights of spleens taken at necropsy and mean concentrations of hemoglobin and mean counts of red and white blood cells from tail vein samples taken at 7, 30, and 90 days are presented in Table 4. A complete spectrum of tissues from all test animals was processed, and all tissues from the control, 2,000-, and 4,000-ppm groups were examined microscopically as well as the spleen, thymus, lymph nodes, and bone marrow from the groups fed 250, 500, or 1,000 ppm.

Gross lesions observed at necropsy included varying degrees of splenomegaly in all dosed groups. This change was dose related with the spleens being larger, heavier, darker, and firmer than the control spleens. In male rats, an increase in the mean weights of spleens occurred at 1,000 ppm, and the mean spleen weight at 4,000 ppm was twice that of the control. In female rats, the mean weight of spleens in the group receiving 250 ppm was greater than that of the control, and those of the groups receiving 2,000 ppm or 4,000 ppm were respectively twice and almost three times that of the control. A dose-related increased incidence of red blood cells with polychromasia and anisocytosis was observed for both male and female rats. Microscopically, the pathologic changes were congestion of the red pulp with corresponding decrease of white pulp.

Concern about the ability of the dosed rats to withstand spleen damage during the chronic 2-year study influenced selecting 125 and 250 ppm as the doses for rats.

Fluometuron was not toxic in mice used in the subchronic study. All mice in the subchronic study survived for 90 days, except one female mouse receiving 500 ppm that died during week 5. Gains in mean body weights were depressed in excess of 10% of the controls in males and females at doses of 4,000 ppm and greater. Feed consumption was normal at all levels. Gross and microscopic examinations revealed no pathologic changes in test or control mice.

Table 3. Doses, Survival, and Mean Body Weights of Rats Fed Fluometuron in the Second 90-Day Subchronic Study

Dose (ppm)	Survival (a)	Mean Body Weights (grams) Initial	Final	Gain	Weight Change Relative to Controls (b) (Percent)
MALES					
0	10/10	106	314	208	
250	10/10	119	294	175	-16
500	10/10	115	301	186	-11
1,000	10/10	112	308	196	-6
2,000	10/10	114	303	188	-10
4,000	10/10	115	290	175	-16
FEMALES					
0	10/10	97	189	91	
250	10/10	98	192	94	+3
500	10/10	99	193	94	+3
1,000	10/10	98	194	96	+5
2,000	10/10	96	186	90	-1
4,000	10/10	95	175	80	-12

(a) Number surviving/number per group.
(b) Weight Change Relative to Controls =

$$\frac{\text{Weight Gain (Dosed Group)} - \text{Weight Gain (Control Group)}}{\text{Weight Gain (Control Group)}} \times 100$$

Table 4. Mean Weights of Spleen, Mean Concentrations of Hemoglobin, and Mean Counts of Red and White Blood Cells in Rats Administered Fluometuron in the Second 90-Day Subchronic Study

Dose (ppm)	Spleen Weight(a) (grams)	Hemoglobin(a) (g/dl)	Red Blood Cell(a) ($\times 10^6/\mu l$)	White Blood Cell(a) (per μl)
MALE				
0	0.60±0.06	16.28±0.71	8.49±0.45	10,400±3,884
250	0.54±0.02	16.34±0.76	8.05±0.45	6,920±1,494
500	0.59±0.04	15.16±1.30	7.41±0.61	5,655±1,770
1,000	0.65±0.04	15.56±0.56	8.15±0.32	6,920±2,115
2,000	0.77±0.03	15.16±0.53	7.44±0.35	8,170±3,105
4,000	1.19±0.10	14.70±0.33	6.61±0.18	9,510±2,676
FEMALE				
0	0.41±0.03	15.75±0.50	8.22±0.58	7,400±3,355
250	0.47±0.04	15.08±0.33	7.05±0.23	6,730±2,523
500	0.50±0.03	14.85±0.31	6.94±0.28	5,475±1,380
1,000	0.63±0.04	14.86±0.54	6.80±0.32	5,770±1,008
2,000	0.84±0.06	14.30±0.46	6.33±0.27	7,110±2,488
4,000	1.11±0.07	14.40±0.74	6.05±0.23	5,770±1,136

(a) Mean Value $\pm$ Standard Deviation.

The low and high doses for the chronic studies were set at 500 ppm and 1,000 ppm for the mice.

F. Chronic Studies

The number of animals per group, doses administered, and durations of the chronic studies are shown in Table 5.

G. Clinical Examinations and Pathology

Animals were observed twice daily and observations of sick, tumor-bearing, and moribund animals were recorded. Animals were weighed and palpated for masses at 2-week intervals. Moribund animals and animals that survived to the end of the bioassay were killed using pentobarbitol and necropsied.

Gross and microscopic examinations were performed on major tissues, major organs, and all gross lesions from killed animals and from animals found dead. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Sections from the tissues were examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, gallbladder (mice), pancreas, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, and brain. Special staining techniques were utilized as necessary. Blood smears of all animals were routinely prepared.

Necropsies were performed on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals for which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

Table 5. Experimental Design of Chronic Feeding Studies with Fluometuron in Rats and Mice

Test Group	Initial No. of Animals(a)	Fluometuron in Diet(b) (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male Rats				
Matched-Control	50	0	0	104-105
Low-Dose	50	125	103	0-1
High-Dose	50	250	103	0-1
Female Rats				
Matched-Control	50	0	0	104-105
Low-Dose	50	125	103	1-2
High-Dose	50	250	103	0-1
Male Mice				
Matched-Control	25	0	0	105
Low-Dose	50	500	103	0-1
High-Dose	50	1,000	103	1-2
Female Mice				
Matched-Control	25	0	0	104-105
Low-Dose	50	500	103	0-1
High-Dose	50	1,000	103	0-1

(a) Rats and mice were approximately 7 weeks old at the start of the study.
(b) Diets were available ad libitum.

H. Data Recording and Statistical Analyses

Data on this experiment have been recorded in a data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is reported only when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors) or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When results for two dosed groups are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 is made. The Bonferroni

inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.025. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

The approximate 95% confidence interval for the relative risk of each dosed group compared with its control was calculated from the exact interval on the odds ratio (Gart, 1971). The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that, in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result has occurred (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero). When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Mean body weights of dosed and control rats were comparable throughout the bioassay (Figure 1). The appearance and behavior of dosed and control rats were generally comparable throughout the study.

At week 63, a majority of both dosed and control animals rejected feed. The rejected feed was discarded and all animals were fed newly mixed control feed. At week 64, after 1 week on the control diet, dosed animals were returned to the dosed diets.

B. Survival (Rats)

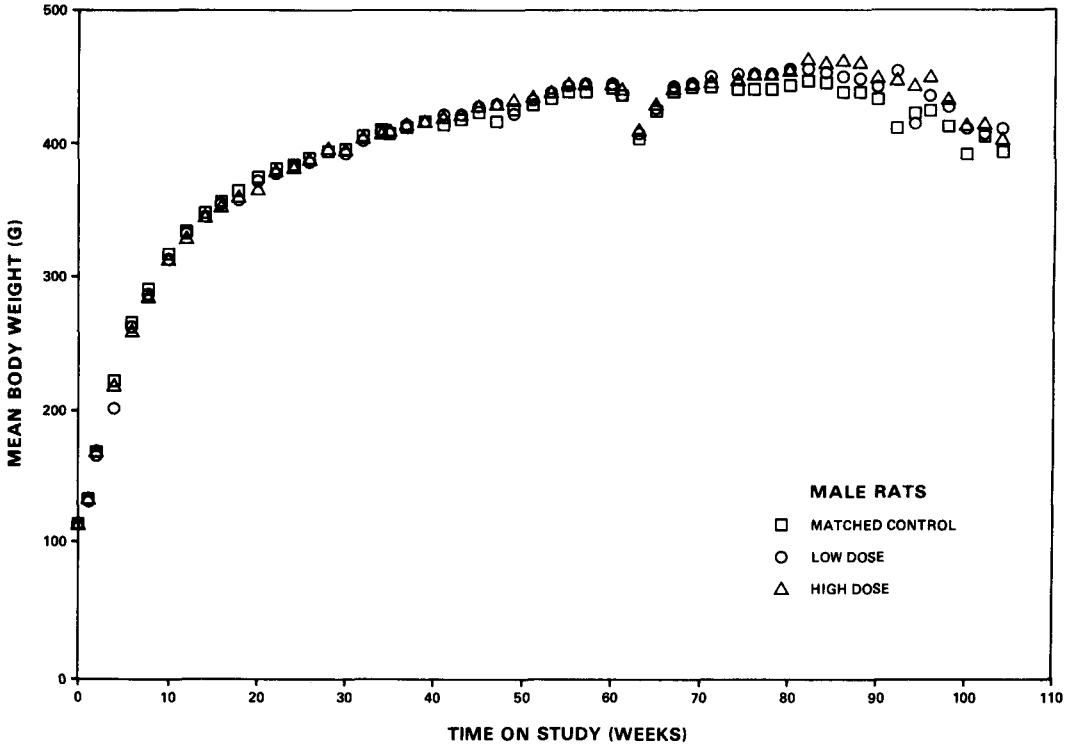
Estimates of the probabilities of survival for male and female rats administered fluometuron in the diet at the doses of this bioassay, together with those of the matched controls, are shown by the Kaplan and Meier curves in Figure 2. The result of the Tarone test for dose-related trend in mortality is not significant in either sex. In female rats, the results of the Cox test between the matched-control group and each dosed group are significant (P=0.014), but in the negative direction.

In male rats, 38/50 (76%) of the matched-control group, 37/50 (74%) of the low-dose group, and 44/50 (88%) of the high-dose group were still alive at week 90. In females, 44/50 (88%) of the matched-control group, 47/50 (94%) of the low-dose group, and 48/50 (96%) of the high-dose group were alive at week 90.

Sufficient numbers of rats of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2.



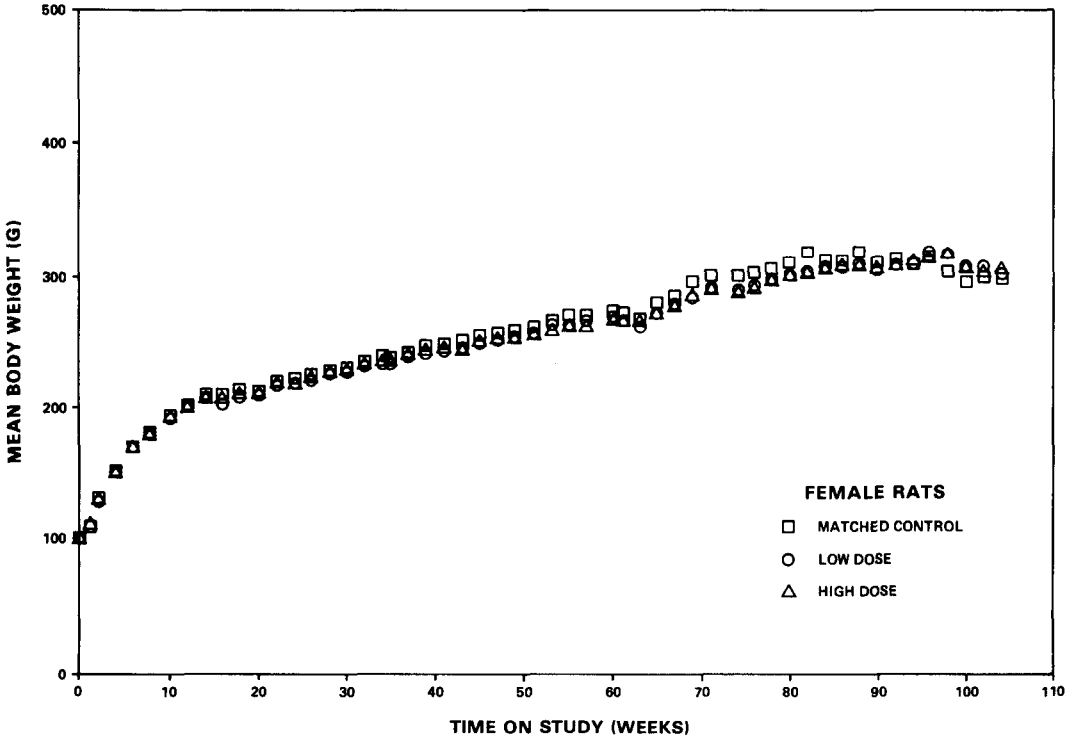


Figure 1. Growth Curves for Rats Administered Fluometuron in the Diet

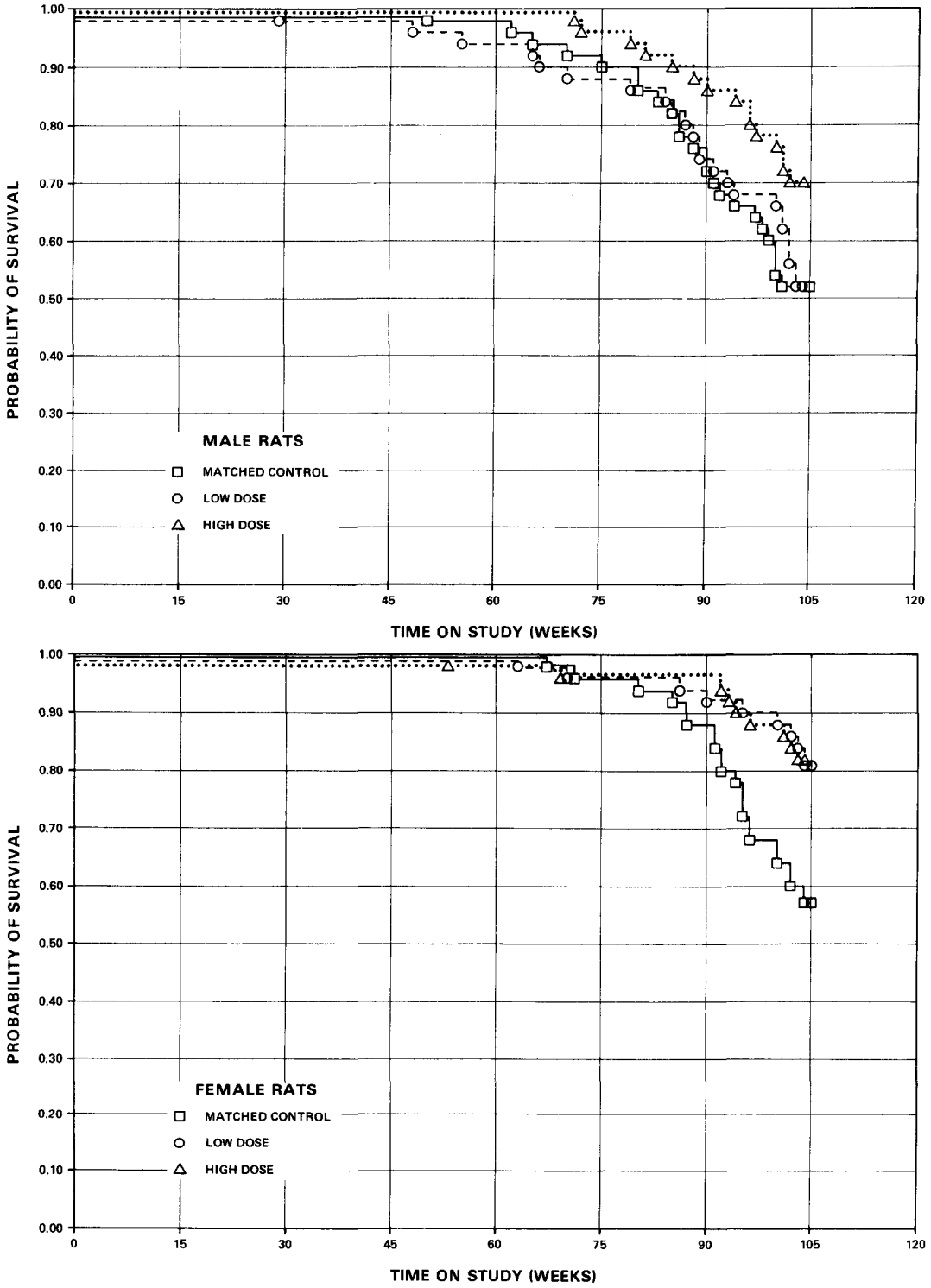


Figure 2. Survival Curves for Rats Administered Fluometuron in the Diet

A variety of neoplasms were observed in control and dosed rats. These neoplasms were of the usual number and type noted in aging F344 rats. Degenerative, proliferative, and inflammatory lesions were also of the usual type and occurred in normal incidences seen in aging F344 rats. No significant lesions were found in the spleens or other bloodforming tissues of dosed rats.

The histopathologic examination did not provide evidence for the carcinogenicity or toxicity of fluometuron in F344 rats under the conditions of this chronic bioassay.

D. Statistical Analyses of Results (Rats)

Tables 6 and 7 contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and at an incidence of at least 5% in one or more groups.

In male rats, the results of the Cochran-Armitage test for positive dose-related trend in the incidences of neoplastic nodules of the liver and chromophobe adenomas of the pituitary are significant, but the results of the Fisher exact test are not significant.

In female rats, a significant dose-related trend in the negative direction (P=0.010) was observed for the incidence of leukemias, but in direct comparisons of dosed with control groups, the incidence of these tumors in the low-dose group was not significantly lower than that in the control group, and the lowered incidence in the high-dose group (P=0.027) did not meet the Bonferroni criterion for significance (P=0.025). Thus, the occurrence of decreased incidences of leukemias in dosed female rats cannot be related statistically to the administration of fluometuron. The historical incidence of control F344 female rats with leukemia under this contract at this laboratory is 40/273 (14.6%).

In each of the 95% confidence intervals for relative risk shown in the tables, the value of one or less than one is included: this indicates the absence of significant positive results. It should also be noted that each of the intervals, except for the incidence of leukemias in high-dose female rats, has an upper limit greater than one, indicating the theoretical possibility of tumor induction by fluometuron, which could not be detected under the conditions of this test.

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Administered Fluometuron in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	3/50 (6)	8/48 (17)	7/50 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		2.778	2.333
Lower Limit		0.714	0.569
Upper Limit		15.403	13.291
Weeks to First Observed Tumor	90	48	85
All Sites: Hemangioma (b)	0/50 (0)	2/48 (4)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		Infinite	Infinite
Lower Limit		0.308	0.601
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	55	104
Liver: Neoplastic Nodule (b)	0/50 (0)	1/48 (2)	4/50 (8)
P Values (c,d)	P=0.027	N.S.	N.S.
Relative Risk (e)		Infinite	Infinite
Lower Limit		0.056	0.927
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	104
Pituitary: Chromophobe Adenoma (b)	12/45 (27)	8/45 (18)	20/48 (42)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.046		
Relative Risk (e)		0.667	1.563
Lower Limit		0.262	0.831
Upper Limit		1.596	3.064
Weeks to First Observed Tumor	70	79	72

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Administered Fluometuron in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Adrenal: Pheochromocytoma (b)	5/50 (10)	4/48 (8)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.833	0.400
Lower Limit		0.175	0.040
Upper Limit		3.638	2.313
Weeks to First Observed Tumor	83	101	104
Thyroid: C-cell Adenoma (b)	4/43 (9)	2/37 (5)	4/48 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.581	0.896
Lower Limit		0.055	0.178
Upper Limit		3.796	4.534
Weeks to First Observed Tumor	99	104	103
Pancreatic Islets: Islet-cell Adenoma (b)	3/50 (6)	1/45 (2)	7/49 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.370	2.381
Lower Limit		0.007	0.581
Upper Limit		4.410	13.550
Weeks to First Observed Tumor	65	104	102
Testis: Interstitial-cell Tumor (b)	42/50 (84)	38/48 (79)	42/50 (84)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.942	1.000
Lower Limit		0.776	0.834
Upper Limit		1.158	1.199
Weeks to First Observed Tumor	80	65	71

(a) Dosed groups received doses of 125 or 250 ppm.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage Test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Administered Fluometuron in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Leukemia (b)	5/49 (10)	1/50 (2)	0/50 (0)
P Values (c,d)	P=0.010 (N)	N.S.	P=0.027 (N)
Departure from Linear Trend (e)	P=0.040		
Relative Risk (f)		0.196	0.000
Lower Limit		0.004	0.000
Upper Limit		1.665	0.777
Weeks to First Observed Tumor	91	86	--
Liver: Neoplastic Nodule (b)	3/49 (6)	3/49 (6)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.000	0.327
Lower Limit		0.140	0.006
Upper Limit		7.126	3.903
Weeks to First Observed Tumor	95	104	104
Pituitary: Chromophobe Adenoma (b)	35/49 (71)	28/48 (58)	30/49 (61)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.817	0.857
Lower Limit		0.598	0.635
Upper Limit		1.128	1.169
Weeks to First Observed Tumor	67	63	53
Thyroid: C-cell Adenoma (b)	5/42 (12)	2/37 (5)	3/45 (7)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.454	0.560
Lower Limit		0.045	0.092
Upper Limit		2.581	2.694
Weeks to First Observed Tumor	96	105	104

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Administered Fluometuron in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma (b)	3/49 (6)	2/50 (4)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.653	0.327
Lower Limit		0.057	0.006
Upper Limit		5.457	3.903
Weeks to First Observed Tumor	92	103	104
Uterus: Endometrial Stromal Polyp (b)	7/47 (15)	12/48 (25)	14/49 (29)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.679	1.918
Lower Limit		0.671	0.801
Upper Limit		4.593	5.112
Weeks to First Observed Tumor	104	70	69

(a) Dosed groups received doses of 125 or 250 ppm.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage Test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.
(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of dosed and control mice were comparable throughout the bioassay (Figure 3). Clinical signs of dosed and control groups were also comparable.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered fluometuron in the diet at the doses of this bioassay, together with those of the matched controls, are shown by the Kaplan and Meier curves in Figure 4. The result of the Tarone test for dose-related trend in mortality is not significant in either sex.

In male mice, 14/25 (56%) of the matched-control group, 33/50 (66%) of the low-dose group, and 32/50 (64%) of the high-dose group lived to the end of the bioassay. In females, 16/25 (64%) of the matched-control group, 38/50 (76%) of the low-dose group, and 33/50 (66%) of the high-dose group lived to the end of the bioassay.

Sufficient numbers of mice of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2.

Neoplastic and nonneoplastic lesions occurred with similar incidences in control and dosed animals with the exception of those of the liver and the hematopoietic system in male mice.

Hepatocellular adenomas or carcinomas were seen in 4/21 (19%) control, 13/47 (28%) low-dose, and 21/49 (43%) high-dose males. The neoplasms in the dosed mice were similar histologically to those in the controls, and there

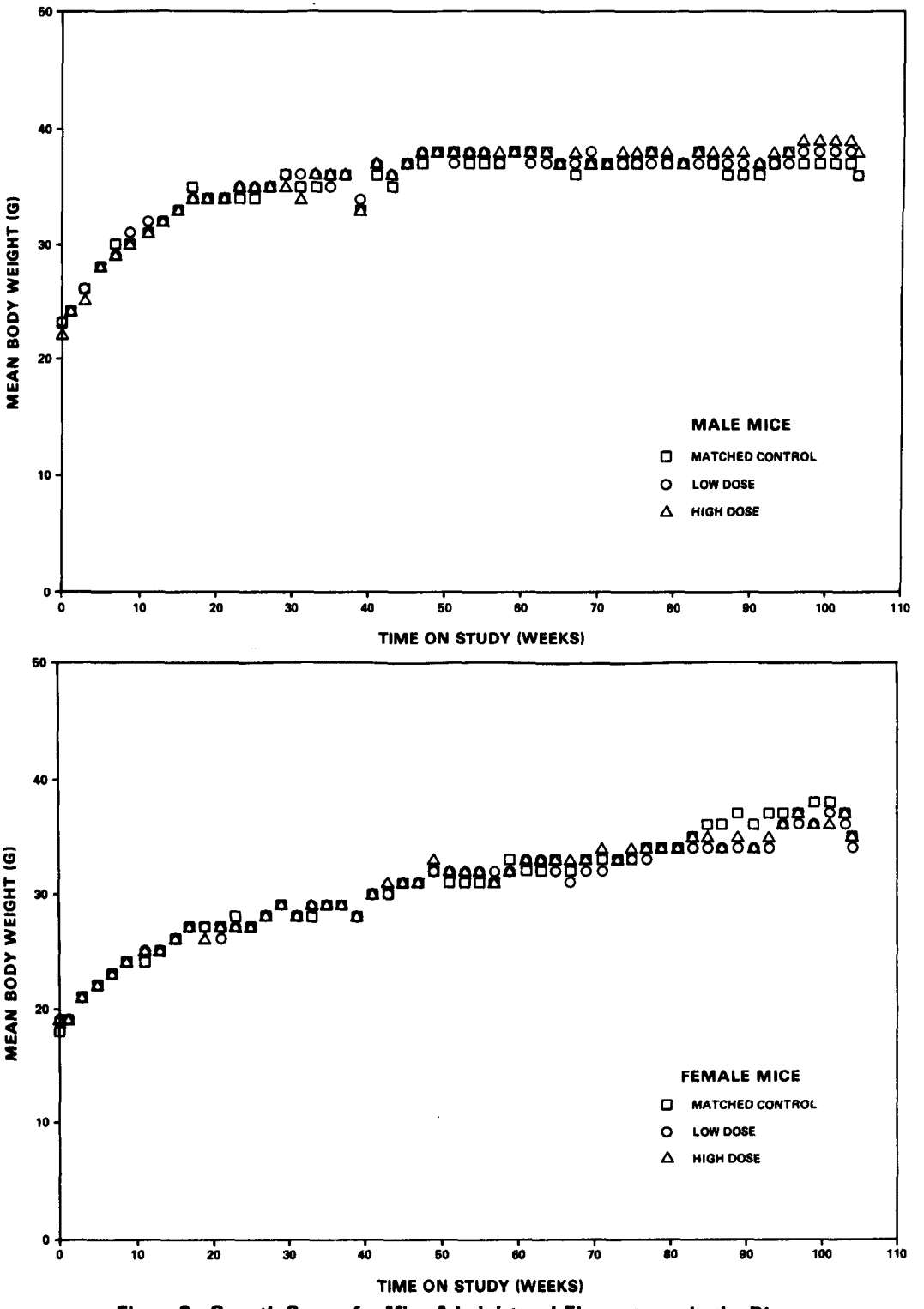


Figure 3. Growth Curves for Mice Administered Fluometuron in the Diet

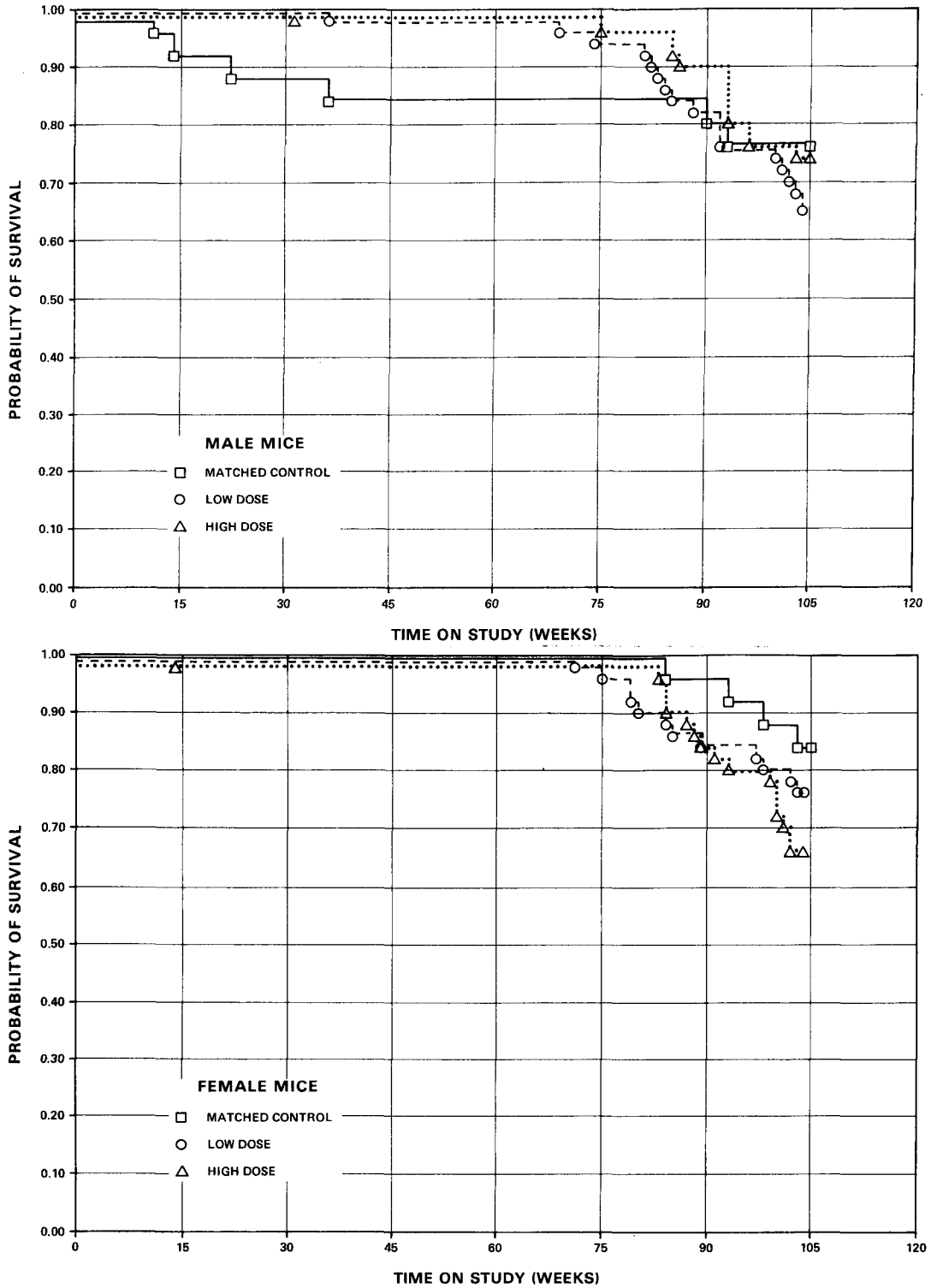


Figure 4. Survival Curves for Mice Administered Fluometuron in the Diet

was no difference in multiplicity of liver tumors between controls and high-dose males. The carcinomas formed trabecular patterns, and one carcinoma in the high-dose males metastasized to the lung.

Lymphomas or leukemias were noted in 0/21 (0%) control, 6/48 (13%) low-dose, and 7/49 (14%) high-dose males.

There were no chemical-related nonneoplastic lesions.

The histopathologic examination provided evidence that fluometuron may induce neoplasms of the liver and hematopoietic system in B6C3F1 male mice under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables 8 and 9 contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and at an incidence of at least 5% in one or more groups. Four of the male control animals died very early in the experiment and were removed from the statistical analysis, leaving 21 male controls.

The incidence of male mice with hepatocellular tumors is significantly higher (P=0.049) in the high-dose group than in the matched-control group. The probability level of P=0.049 is higher than the P=0.025 required by the Bonferroni inequality when two dosed groups are compared with a common control group. This study in mice was conducted for 104 to 105 weeks. A pooled-control group of male mice was formed by grouping the vehicle-control (2% corn oil in feed) animals from fenthion, aldicarb, coumaphos, anilazine, diazinon, and malaoxon studies. These studies were conducted concurrently for 104 to 105 weeks at the same laboratory as fluometuron, were read by the same team of pathologists, and used B6C3F1 mice. The incidence of animals with hepatocellular adenomas in the pooled controls was 44/167 (26%) compared with the high-dose incidence of 21/49 (43%) observed in the male high-dose group of this study; however, the incidence in one of the groups comprising the pooled controls was 9/23 (39%), which is near the 21/49 (43%) observed in the high-dose group in this study. In the other five groups of the pooled controls, the incidence ranged from 21% to 29%.

The statistical conclusion is that the incidence of male mice with hepatocellular adenomas or carcinomas may have been related to the

administration of fluometuron, but this relationship is not clearly established. There were no significant results in the female mice.

In each of the 95% confidence intervals of relative risk, shown in the Tables 8 and 9, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by fluometuron, which could not be detected under the conditions of this test.

Table 8. Analyses of the Incidence of Primary Tumors in Male Mice Administered Fluometuron in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	2/21 (10)	4/48 (8)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.875	1.286
Lower Limit		0.139	0.259
Upper Limit		9.223	12.304
Weeks to First Observed Tumor	105	103	93
Hematopoietic System: Lymphoma or Leukemia (b)	0/21 (0)	6/48 (13)	7/49 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		Infinite	Infinite
Lower Limit		0.727	0.864
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	36	75
Liver: Hepatocellular Carcinoma (b)	3/21 (14)	8/47 (17)	15/49 (31)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		1.191	2.143
Lower Limit		0.328	0.705
Upper Limit		6.484	10.656
Weeks to First Observed Tumor	93	82	85
Liver: Hepatocellular Carcinoma or Adenoma (b)	4/21 (19)	13/47 (28)	21/49 (43)
P Values (c,d)	P=0.024	N.S.	P=0.049
Relative Risk (e)		1.452	2.250
Lower Limit		0.527	0.901
Upper Limit		5.548	8.076
Weeks to First Observed Tumor	93	82	85

(a) Dosed groups received doses of 500 or 1,000 ppm.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage Test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the control group.

Table 9. Analyses of the Incidence of Primary Tumors in Female Mice Administered Fluometuron in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	5/21 (20)	8/48 (17)	13/49 (27)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.833	1.327
Lower Limit		0.275	0.514
Upper Limit		2.956	4.304
Weeks to First Observed Tumor	98	75	83
Liver: Hepatocellular Carcinoma or Adenoma (b)	1/25 (4)	3/48 (6)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		1.563	2.041
Lower Limit		0.135	0.219
Upper Limit		80.301	98.444
Weeks to First Observed Tumor	105	85	99

(a) Dosed groups received doses of 500 or 1,000 ppm.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage Test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the control group.

V. DISCUSSION

Dose-related effects such as decreased numbers of circulating red blood cells, acutely congested and enlarged spleens, and increased numbers of red blood cells with polychromasia and anisocytosis were observed in rats during the second 90-day study with fluometuron. Incidences of splenomegalia in rats associated with the lowest doses of the test chemical were 5/10 in females fed 200 ppm and 2/10 in males fed 500 ppm. Mean weights of spleens were elevated in male rats administered 1,000 ppm fluometuron and were twice those of the controls in males administered 4,000 ppm. In female rats, a dose-related increase in mean weights of spleens occurred at all doses; mean weights of spleens were twice those of the controls in female rats administered 2,000 ppm and almost tripled in female rats administered 4,000 ppm. Splenomegaly was not reported in mice. Concern about the ability of the dosed rats to withstand spleen damage, during the chronic 2-year study, influenced setting the doses in rats at 125 and 250 ppm. Doses for the mice were 500 and 1,000 ppm. Since mean body weights and survival of all groups of rats and mice in the chronic study were similar to those of their corresponding controls, these animals probably could have tolerated higher doses.

The doses selected for the chronic study in rats did not induce the splenic effects observed in the subchronic studies. In male rats, significant dose-related trends in the positive direction (P less than or equal to 0.016) were observed for the incidences of neoplastic nodules of the liver and chromophobe adenomas of the pituitary gland. However, since in direct comparisons the incidences in individual dosed groups were not significantly higher than those in corresponding controls, the occurrence of these tumors at the doses used in the male rats cannot be related statistically to administration of fluometuron.

In male mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related (P=0.024), and in a direct comparison, the incidence of these tumors in the high-dose group was significantly higher (P=0.049) than those of the corresponding control group. The incidence in the high-dose group is also significantly higher (P=0.020) than those of the pooled controls; however, the incidence in one of the groups comprising the

pooled controls was 9/23 (39%), which is near the 21/49 (43%) observed in the high-dose group in this study. The results are considered suggestive but not conclusive.

In female mice, no tumors occurred at incidences that differed significantly among the dosed and control groups.

Under the conditions of this bioassay, fluometuron was not carcinogenic for either sex of F344 rats or female B6C3F1 mice. Although the incidence of hepatocellular adenomas and carcinomas in male mice was dose related with the number in the high-dose group being significantly greater than the matched control, the importance of these observations was decreased by occurrences of similar incidences among select groups in the pooled historical controls.

VI. BIBLIOGRAPHY

Armitage, P., Statistical Methods in Medical Research, John Wiley & Sons, Inc., New York, 1971, pp. 362-365.

Berenblum, I., ed., Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2, International Union Against Cancer, Geneva, 1969.

CIBA-GEIGY Corporation, Herbicidal preparations containing N-(3- and 4-trifluoromethyl-phenyl)-N',N'-dimethylurea. CIBA Ltd., Brit. 914, 779, January 2, 1963.

CIBA-GEIGY Corporation, Cotoran® (Brand of fluometuron), Agricultural Division, CIBA-GEIGY Corporation, Ardsley, N.Y. , 1972.

Cox, D. R., Regression models and life tables. J. R. Statist. Soc. B 34:187-220, 1972.

Cox, D. R., Analysis of Binary Data, Methuen & Co., Ltd., London, 1970, pp. 48-52.

EPA, Environmental Protection Agency, Fluometuron. In: EPA Compendium of Registered Pesticides I-F-11.1, Environmental Protection Agency, Washington, D. C., 1970.

Gart, J. J., The comparison of proportions: a review of significance tests, confidence limits and adjustments for stratification., Rev. Int. Stat. Inst. 39:148-169, 1971.

Kaplan, E. L. and Meier, P., Nonparametric estimation from incomplete observations. J. Amer. Statist. Assoc. 53:457-481, 1958.

Lin, T. H., Menzer, R. E., and North, H. H., Metabolism in human embryonic lung cell cultures of three phenylurea herbicides: chlorotoluron, fluometuron, and metobromuron. J. Agric. Food Chem. 24:759-763, 1976.

Linhart, M. S., Cooper, J. A., Martin, R. L., Page, N. P., and Peters, J. A., Carcinogenesis bioassay data system. Comp. and Biomed. Res. 7:230-248, 1974.

Martin, H. and Worthing, C. R., eds., Fluometuron. In: Pesticide Manual, British Crop Protection Council, London, 1977, p. 277.

Meister, R. J., ed., Cotoran®. In: 1977 Farm Chemicals Handbook, Meister Publishing Co., Willougby, Ohio, 1977, p. D 70.

Melnekov, N. N., Derivatives of urea and thiourea. In: Chemistry of Pesticides, Springer-Verlag, New York, 1971, pp. 225-236.

Merck Index, Stecher, P.G., ed., Merck & Co., Inc., Rahway, N.J., 1976.

Miller, R. G., Jr., Simultaneous Statistical Inference, McGraw-Hill Book Co., New York, 1966, pp. 6-10.

Muecke, W., Menzer, R. E., Alt, K. O., Richter, W., and Esser, H. O., The metabolism of chlorotoluron in the rat. Pestic. Biochem. Physiol. 6:430-441, 1976.

NCI, National Cancer Institute, Guidelines for Carcinogen Bioassay in Small Rodents, Technical Report No. 1, DHEW Publication No. (NIH) 76-801, U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Bethesda, Md., 1976.

Seiler, J. P., Herbicidal phenylalkylureas as possible mutagens: I. Mutagenicity tests with some urea herbicides. Mutat. Res. 59 (2/3): 353-359, 1978.

Spencer, E. Y., Fluometuron. In: Guide to the Chemicals Used in Crop Protection, Information Canada, Ottawa, Canada, 1973, p. 283.

Tarone, R. E., Tests for trend in life table analysis. Biometrika 62 (3):679-682, 1975.

U. S. Department of Agriculture, Farmers' Use of Pesticides in 1971, Agricultural Economics Report No. 252, Economic Research Service, U. S. Department of Agriculture, Washington, D. C., 1974.

U. S. Department of Agriculture, Farmers' Use of Pesticides in 1976, Agricultural Economics Report No. 418, Economic Statistics and Cooperatives Service, U. S. Department of Agriculture, Washington, D. C., 1978.

Warzok, R., Thust, R., Mendel, J., Schwarz, H., and Blaufuss, E., Methylnitrosophenylurea - a highly carcinogenic compound. Cancer Letters 4:299-303, 1978.

Weed Society of America, Personal Communication, 21 March 1979.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED FLUOMETURON IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED FLUOMETURON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(48)	(50)
PAPILLOMA, NOS	1 (2%)		
BASAL-CELL TUMOR		1 (2%)	
FIBROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(47)	(49)
SQUAMOUS CELL CARCINOMA	1 (2%)		
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(48)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
LEUKEMIA,NOS		1 (2%)	5 (10%)
UNDIFFERENTIATED LEUKEMIA		1 (2%)	
MONOCYTIC LEUKEMIA	3 (6%)	5 (10%)	2 (4%)
CIRCULATORY SYSTEM			
*AXILLA	(50)	(48)	(50)
HEMANGIOMA		1 (2%)	
#SPLEEN	(50)	(46)	(48)
HEMANGIOMA		1 (2%)	3 (6%)
DIGESTIVE SYSTEM			
*LIP	(50)	(48)	(50)
FIBROSARCOMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(50)	(48)	(50)
NEOPLASTIC NODULE		1 (2%)	4 (8%)
#COLON	(45)	(48)	(46)
ADENOCA IN ADENOMATOUS POLYP			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(45)	(48)
CARCINOMA,NOS	1 (2%)		1 (2%)
CHROMOPHOBE ADENOMA	12 (27%)	8 (18%)	20 (42%)
MIXED TUMOR, BENIGN	1 (2%)	1 (2%)	
#ADRENAL	(50)	(48)	(50)
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA	5 (10%)	4 (8%)	2 (4%)
GANGLIONEUROMA	1 (2%)		
#THYROID	(43)	(37)	(48)
FOLLICULAR-CELL CARCINOMA		1 (3%)	
C-CELL ADENOMA	4 (9%)	2 (5%)	4 (8%)
#PANCREATIC ISLETS	(50)	(45)	(49)
ISLET-CELL ADENOMA	3 (6%)	1 (2%)	7 (14%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(48)	(50)
FIBROMA	1 (2%)		1 (2%)
FIBROADENOMA		1 (2%)	
#TESTIS	(50)	(48)	(50)
INTERSTITIAL-CELL TUMOR	42 (84%)	38 (79%)	42 (84%)
NERVOUS SYSTEM			
#CEREBELLUM	(50)	(47)	(50)
MENINGIOMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*TRIGEMINAL NERVE	(50)	(48)	(50)
NEURILEMOMA			1 (2%)
NEURILEMOMA, MALIGNANT	1 (2%)		
SPECIAL SENSE ORGANS			
*EXTERNAL EAR	(50)	(48)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(48)	(50)
OSTEOMA	1 (2%)		
BODY CAVITIES			
*PERITONEUM	(50)	(48)	(50)
MESOTHELIOMA BENIGN	1 (2%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	5	8	4
MORIBUND SACRIFICE	19	16	13
SCHEDULED SACRIFICE	2		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	24	26	33
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	48	44	50
TOTAL PRIMARY TUMORS	82	68	94
TOTAL ANIMALS WITH BENIGN TUMORS	47	43	50
TOTAL BENIGN TUMORS	73	58	81
TOTAL ANIMALS WITH MALIGNANT TUMORS	8	9	9
TOTAL MALIGNANT TUMORS	9	9	9
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	4
TOTAL UNCERTAIN TUMORS		1	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED FLUOMETURON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
BASAL-CELL TUMOR			1 (2%)
KERATOACANTHOMA		1 (2%)	
FIBROMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)
CHORDOMA METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
LEUKEMIA,NOS	1 (2%)		
UNDIFFERENTIATED LEUKEMIA	1 (2%)	1 (2%)	
MONOCYTIC LEUKEMIA	3 (6%)		
CIRCULATORY SYSTEM			
#LIVER	(49)	(49)	(50)
HEMANGIOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(49)	(50)
NEOPLASTIC NODULE	3 (6%)	3 (6%)	1 (2%)
#PANCREAS	(48)	(48)	(50)
FIBROMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#STOMACH	(48)	(47)	(49)
ENDOMETRIAL STROMAL SARCOMA, MET			1 (2%)
#SMALL INTESTINE	(46)	(48)	(47)
ENDOMETRIAL STROMAL SARCOMA, MET			1 (2%)
URINARY SYSTEM			
*URETER	(49)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA, MET		1 (2%)	
#URINARY BLADDER	(45)	(46)	(50)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(48)	(49)
CARCINOMA,NOS		1 (2%)	
CHROMOPHOBE ADENOMA	35 (71%)	28 (58%)	30 (61%)
#ADRENAL	(49)	(48)	(49)
CORTICAL ADENOMA	1 (2%)	2 (4%)	1 (2%)
PHEOCHROMOCYTOMA	2 (4%)	2 (4%)	1 (2%)
#THYROID	(42)	(37)	(45)
C-CELL ADENOMA	5 (12%)	2 (5%)	3 (7%)
#PANCREATIC ISLETS	(48)	(48)	(50)
ISLET-CELL ADENOMA	1 (2%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
UNDIFFERENTIATED CARCINOMA			1 (2%)
ADENOCARCINOMA, NOS	2 (4%)		1 (2%)
PAPILLARY ADENOCARCINOMA		1 (2%)	2 (4%)
SWEAT GLAND CARCINOMA	1 (2%)		
FIBROADENOMA	3 (6%)	2 (4%)	1 (2%)
#UTERUS	(47)	(48)	(49)
LEIOMYOMA		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ENDOMETRIAL STROMAL POLYP	7 (15%)	12 (25%)	14 (29%)
ENDOMETRIAL STROMAL SARCOMA			2 (4%)
#OVARY	(49)	(47)	(50)
FIBROSARCOMA			1 (2%)
ENDOMETRIAL STROMAL SARCOMA, MET			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(49)	(50)	(50)
CHORDOMA			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	3	3	1
MORIBUND SACRIFICE	18	6	8
SCHEDULED SACRIFICE	2	2	
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	27	39	41
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	45	41	42
TOTAL PRIMARY TUMORS	66	58	64
TOTAL ANIMALS WITH BENIGN TUMORS	42	40	41
TOTAL BENIGN TUMORS	55	51	55
TOTAL ANIMALS WITH MALIGNANT TUMORS	8	4	7
TOTAL MALIGNANT TUMORS	8	4	8
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	2
TOTAL SECONDARY TUMORS		1	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3	3	1
TOTAL UNCERTAIN TUMORS	3	3	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED FLUOMETURON IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED FLUOMETURON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	48	49
INTEGUMENTARY SYSTEM			
*SKIN	(25)	(48)	(49)
FIBROMA	1 (4%)	2 (4%)	
*SUBCUT TISSUE	(25)	(48)	(49)
FIBROSARCOMA	1 (4%)	1 (2%)	
FIBROUS HISTIOCYTOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(25)	(48)	(49)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (8%)	4 (8%)	6 (12%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(25)	(48)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	2 (4%)
LEUKEMIA,NOS			1 (2%)
LYMPHOCYTIC LEUKEMIA		2 (4%)	
GRANULOCYTIC LEUKEMIA		1 (2%)	
#MESENTERIC L. NODE	(24)	(46)	(45)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#JEJUNUM	(19)	(42)	(47)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)
CIRCULATORY SYSTEM			
#SPLEEN	(25)	(48)	(46)
HEMANGIOMA			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(25)	(47)	(49)
HEMANGIOMA	1 (4%)		
DIGESTIVE SYSTEM			
#LIVER	(25)	(47)	(49)
HEPATOCELLULAR ADENOMA	1 (4%)	5 (11%)	6 (12%)
HEPATOCELLULAR CARCINOMA	3 (12%)	8 (17%)	15 (31%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#TESTIS	(25)	(48)	(49)
INTERSTITIAL-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(25)	(48)	(49)
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@	3	8	3
MORIBUND SACRIFICE	3	9	10
SCHEDULED SACRIFICE	5		5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	33	32
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	27	29
TOTAL PRIMARY TUMORS	9	28	36
TOTAL ANIMALS WITH BENIGN TUMORS	5	13	13
TOTAL BENIGN TUMORS	5	13	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	15	20
TOTAL MALIGNANT TUMORS	4	15	22
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED FLUOMETURON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	48	49
INTEGUMENTARY SYSTEM			
*SKIN	(25)	(48)	(49)
CARCINOMA,NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(25)	(47)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (4%)	1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(25)	(48)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	3 (12%)		3 (6%)
LEUKEMIA,NOS	1 (4%)	2 (4%)	5 (10%)
LYMPHOCYTIC LEUKEMIA		2 (4%)	1 (2%)
MONOCYTIC LEUKEMIA			1 (2%)
#SPLEEN	(24)	(47)	(47)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (4%)		
#MESENTERIC L. NODE	(23)	(39)	(45)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (3%)	1 (2%)
#LIVER	(25)	(48)	(49)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
#DUODENUM	(22)	(41)	(44)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#JEJUNUM	(22)	(41)	(44)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*SKIN	(25)	(48)	(49)
HEMANGIOSARCOMA	1 (4%)		
#LIVER	(25)	(48)	(49)
HEMANGIOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(25)	(48)	(49)
HEPATOCELLULAR ADENOMA		1 (2%)	3 (6%)
HEPATOCELLULAR CARCINOMA	1 (4%)	2 (4%)	1 (2%)
#STOMACH	(25)	(45)	(48)
PAPILLOMA, NOS			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(34)	(33)
ADENOMA, NOS		1 (3%)	
CHROMOPHOBE ADENOMA	1 (5%)		1 (3%)
#ADRENAL	(24)	(47)	(48)
CORTICAL ADENOMA			1 (2%)
#THYROID	(22)	(45)	(46)
FOLLICULAR-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(48)	(49)
ADENOCARCINOMA, NOS			2 (4%)
#UTERUS	(25)	(44)	(46)
LEIOMYOMA			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ENDOMETRIAL STROMAL POLYP		1 (2%)	1 (2%)
MESENCHYMOMA, METASTATIC			1 (2%)
#OVARY	(24)	(45)	(49)
PAPILLARY CYSTADENOMA, NOS			1 (2%)
TERATOMA, BENIGN	1 (4%)		1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(25)	(48)	(49)
ALVEOLAR/BRONCHIOLAR CA, INVASIV		1 (2%)	
*ABDOMINAL WALL	(25)	(48)	(49)
MESENCHYMOMA, MALIGNANT			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@		5	6
MORIBUND SACRIFICE	4	7	11
SCHEDULED SACRIFICE	5		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	38	33
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	15	23
TOTAL PRIMARY TUMORS	10	16	30
TOTAL ANIMALS WITH BENIGN TUMORS	2	3	10
TOTAL BENIGN TUMORS	3	4	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	12	16
TOTAL MALIGNANT TUMORS	7	12	17
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED FLUOMETURON IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED FLUOMETURON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(48)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(47)	(49)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
PNEUMONIA, CHRONIC MURINE	1 (2%)		
CALCIFICATION, METASTATIC	1 (2%)	1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MAMMARY GLAND	(50)	(48)	(50)
DYSPLASIA, NOS	1 (2%)		
#SPLEEN	(50)	(46)	(48)
CONGESTION, NOS	1 (2%)		
HEMORRHAGE	1 (2%)		
FIBROSIS, FOCAL		1 (2%)	
INFARCT, NOS		1 (2%)	
HEMATOPOIESIS		1 (2%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(48)	(50)
PERIARTERITIS	1 (2%)		
#LUNG	(50)	(47)	(49)
THROMBOSIS, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#HEART	(50)	(47)	(50)
THROMBUS, ORGANIZED	1 (2%)		
CALCIFICATION, METASTATIC		1 (2%)	2 (4%)
#LEFT ATRIUM	(50)	(47)	(50)
THROMBUS, ORGANIZED	1 (2%)	1 (2%)	
#LEFT AURICULAR APPEN	(50)	(47)	(50)
THROMBOSIS, NOS		1 (2%)	
THROMBUS, ORGANIZED	2 (4%)	2 (4%)	
#MYOCARDIUM	(50)	(47)	(50)
FIBROSIS, MULTIFOCAL	4 (8%)	3 (6%)	3 (6%)
FIBROSIS, DIFFUSE	1 (2%)		
NECROSIS, FOCAL		1 (2%)	
*ARTERY	(50)	(48)	(50)
MEDIAL CALCIFICATION	1 (2%)		
*CORONARY ARTERY	(50)	(48)	(50)
MEDIAL CALCIFICATION	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(48)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#LIVER	(50)	(48)	(50)
CONGESTION, PASSIVE	1 (2%)		
NECROSIS, FOCAL	1 (2%)	1 (2%)	
NECROSIS, DIFFUSE			1 (2%)
INFARCT, FOCAL			1 (2%)
METAMORPHOSIS FATTY	6 (12%)	4 (8%)	6 (12%)
FOCAL CELLULAR CHANGE	4 (8%)	1 (2%)	1 (2%)
HYPERPLASIA, DIFFUSE			1 (2%)
#BILE DUCT	(50)	(48)	(50)
INFLAMMATION, CHRONIC	2 (4%)		
INFLAMMATION, CHRONIC FOCAL	3 (6%)	2 (4%)	2 (4%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	3 (6%)	3 (6%)	
#PANCREAS	(50)	(45)	(49)
INFLAMMATION, CHRONIC	2 (4%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
FIBROSIS, FOCAL		1 (2%)	2 (4%)
FIBROSIS, DIFFUSE			2 (4%)
ATROPHY, NOS		1 (2%)	1 (2%)
ATROPHY, FOCAL		1 (2%)	1 (2%)
HYPERTROPHY, FOCAL			1 (2%)
#STOMACH	(48)	(48)	(46)
ULCER, ACUTE	1 (2%)	1 (2%)	
ULCER, PERFORATED			2 (4%)
CALCIFICATION, METASTATIC	2 (4%)	2 (4%)	1 (2%)
#INTESTINAL VILLUS	(47)	(47)	(45)
ATROPHY, NOS		1 (2%)	
#DUODENUM	(47)	(47)	(45)
DIVERTICULUM			1 (2%)
*RECTUM	(50)	(48)	(50)
ABSCESS, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(50)
INFLAMMATION, CHRONIC	45 (90%)	41 (85%)	46 (92%)
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(45)	(48)
CYST, NOS			1 (2%)
HEMORRHAGE		3 (7%)	
HYPERPLASIA, FOCAL	2 (4%)	4 (9%)	4 (8%)
#ADRENAL CORTEX	(50)	(48)	(50)
HYPERPLASIA, FOCAL			1 (2%)
#ADRENAL MEDULLA	(50)	(48)	(50)
HYPERPLASIA, NODULAR	3 (6%)	3 (6%)	2 (4%)
#THYROID	(43)	(37)	(48)
HYPERPLASIA, C-CELL	1 (2%)	1 (3%)	1 (2%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		2 (4%)
#PARATHYROID	(33)	(26)	(38)
HYPERPLASIA, NOS	2 (6%)		1 (3%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, SECONDARY	2 (6%)	1 (4%)	2 (5%)
#PANCREATIC ISLETS	(50)	(45)	(49)
HYPERPLASIA, FOCAL		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(48)	(50)
METAPLASIA, OSSEOUS	1 (2%)		
#PROSTATE	(46)	(46)	(50)
INFLAMMATION, SUPPURATIVE	2 (4%)		
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
ABSCESS, NOS			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#TESTIS	(50)	(48)	(50)
ATROPHY, NOS		1 (2%)	
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(50)	(47)	(50)
GLIOSIS			1 (2%)
INFARCT, NOS		1 (2%)	1 (2%)
INFARCT, FOCAL		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(48)	(50)
FIBROUS OSTEODYSTROPHY	1 (2%)		
BODY CAVITIES			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(48)	(50)
CALCIFICATION, METASTATIC	1 (2%)		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	
AUTOLYSIS/NO NECROPSY		2	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED FLUOMETURON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#SPLEEN	(49)	(48)	(50)
FIBROSIS, FOCAL			1 (2%)
INFARCT, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#RIGHT ATRIUM	(49)	(49)	(50)
THROMBUS, ORGANIZED	1 (2%)		
#MYOCARDIUM	(49)	(49)	(50)
FIBROSIS, FOCAL	1 (2%)		
FIBROSIS, MULTIFOCAL	1 (2%)		
DEGENERATION, NOS	1 (2%)		
#ENDOCARDIUM	(49)	(49)	(50)
FIBROSIS, FOCAL		1 (2%)	
#UTERUS	(47)	(48)	(49)
THROMBUS, ORGANIZED			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(49)	(50)
INFLAMMATION, FOCAL GRANULOMATOU	4 (8%)		1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, DIFFUSE			1 (2%)
INFARCT, FOCAL	1 (2%)		
METAMORPHOSIS FATTY	4 (8%)	3 (6%)	2 (4%)
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	8 (16%)
#BILE DUCT	(49)	(49)	(50)
INFLAMMATION, CHRONIC FOCAL	2 (4%)	1 (2%)	
#PANCREAS	(48)	(48)	(50)
ATROPHY, NOS		1 (2%)	2 (4%)
ATROPHY, DIFFUSE		1 (2%)	
#STOMACH	(48)	(47)	(49)
DIVERTICULUM			1 (2%)
ULCER, ACUTE		1 (2%)	
EROSION	1 (2%)		
ULCER, PERFORATED	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
INFLAMMATION, CHRONIC	39 (80%)	26 (52%)	30 (60%)
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(48)	(49)
CYST, NOS	1 (2%)	3 (6%)	3 (6%)
HEMORRHAGE	4 (8%)	2 (4%)	2 (4%)
HYPERPLASIA, FOCAL	8 (16%)	5 (10%)	5 (10%)
#ADRENAL CORTEX	(49)	(48)	(49)
CYST, NOS		1 (2%)	
METAMORPHOSIS FATTY	1 (2%)	1 (2%)	2 (4%)
HYPERPLASIA, FOCAL	1 (2%)	2 (4%)	
#ADRENAL MEDULLA	(49)	(48)	(49)
HYPERPLASIA, NODULAR	2 (4%)	1 (2%)	
#THYROID	(42)	(37)	(45)
HYPERPLASIA, C-CELL	1 (2%)	3 (8%)	1 (2%)
HYPERPLASIA, FOLLICULAR-CELL			2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
ABSCESS, NOS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, CYSTIC	23 (47%)	12 (24%)	9 (18%)
*MAMMARY LOBULE	(49)	(50)	(50)
HYPERPLASIA, NOS	4 (8%)	2 (4%)	4 (8%)
#OVARY	(49)	(47)	(50)
CYST, NOS		1 (2%)	
NERVOUS SYSTEM			
#CEREBRUM	(47)	(49)	(50)
INFARCT, HEALED		1 (2%)	
#BRAIN	(47)	(49)	(50)
GLIOSIS	1 (2%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		2	1
AUTOLYSIS/NO NECROPSY	1		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED FLUOMETURON IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED FLUOMETURON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	48	49
INTEGUMENTARY SYSTEM			
*SKIN	(25)	(48)	(49)
EPIDERMAL INCLUSION CYST		1 (2%)	
FIBROSIS, FOCAL			1 (2%)
CALCIFICATION, METASTATIC			1 (2%)
*SUBCUT TISSUE	(25)	(48)	(49)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#LYMPH NODE	(24)	(46)	(45)
INFLAMMATION, NOS	1 (4%)		
#MESENTERIC L. NODE	(24)	(46)	(45)
INFLAMMATION, NOS	1 (4%)		
#RENAL LYMPH NODE	(24)	(46)	(45)
INFLAMMATION, NOS			1 (2%)
#INGUINAL LYMPH NODE	(24)	(46)	(45)
INFLAMMATION, NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(25)	(47)	(49)
ABSCESS, NOS		1 (2%)	
NECROSIS, FOCAL	1 (4%)		
HYPERPLASIA, NODULAR	1 (4%)		
#HEPATIC LOBULE	(25)	(47)	(49)
INFARCT, NOS		1 (2%)	
#PEYER'S PATCH	(19)	(42)	(47)
INFLAMMATION, NOS	1 (5%)		
URINARY SYSTEM			
#URINARY BLADDER	(23)	(45)	(46)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*PREPUCE	(25)	(48)	(49)
INFLAMMATION, ACUTE/CHRONIC	1 (4%)		
#PROSTATE	(25)	(45)	(47)
HEMORRHAGE		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (4%)		
#TESTIS	(25)	(48)	(49)
ATROPHY, NOS	1 (4%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	13	18	18
AUTO/NECROPSY/HISTO PERF		1	
AUTOLYSIS/NO NECROPSY		2	1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED FLUOMETURON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	48	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(25)	(47)	(49)
ABSCESS, NOS		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (4%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(24)	(47)	(47)
FIBROSIS, FOCAL			1 (2%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(25)	(48)	(49)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
HYPERPLASIA, NODULAR		1 (2%)	
#LIVER/CENTRILOBULAR	(25)	(48)	(49)
DEGENERATION, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#PANCREAS	(25)	(47)	(47)
CYST, NOS			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC	1 (4%)		
INFLAMMATION WITH FIBROSIS		1 (2%)	
NECROSIS, FAT	1 (4%)		
ATROPHY, NOS			1 (2%)
#JEJUNUM	(22)	(41)	(44)
HYPERPLASIA, NOS	1 (5%)		
URINARY SYSTEM			
#PERIRENAL TISSUE	(23)	(44)	(45)
LIPOGRANULOMA			1 (2%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(48)	(49)
ADENOSIS	1 (4%)	3 (6%)	
*MAMMARY LOBULE	(25)	(48)	(49)
HYPERPLASIA, NOS	1 (4%)		1 (2%)
#UTERUS	(25)	(44)	(46)
MUCOCELE			1 (2%)
#UTERUS/ENDOMETRIUM	(25)	(44)	(46)
HYPERPLASIA, CYSTIC	2 (8%)	1 (2%)	2 (4%)
#OVARY	(24)	(45)	(49)
CYST, NOS	3 (13%)	2 (4%)	1 (2%)
FOLLICULAR CYST, NOS		1 (2%)	1 (2%)
ABSCESS, NOS	1 (4%)	1 (2%)	
#OVARY/FOLLICLE	(24)	(45)	(49)
RUPTURE		1 (2%)	
NERVOUS SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	10	21	18
AUTOLYSIS/NO NECROPSY		2	1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

ANALYSIS OF FLUOMETURON

Appendix E

Analysis of Fluometuron

A. Elemental Analysis

Element:	C	H	N	F
Theoretical:	51.73	4.78	12.06	24.54
Measured:	51.66	4.69	12.00	24.51

B. Melting Point

Literature: 163^{o}-164.5^{o}C (Merck, 1976)

Measured: 156^{o}-158^{o}C

C. Thin-Layer Chromatography

Plate: Silica gel G-250, activated at 130^{o}C

Visualization: Long and short wavelength uv and I_2 vapor

System 1: Benzene: MeOH (4:1)

Results: Single spot with R_f of 0.496

System 2: Hexane: EtOAc:MeOH (3:1:1)

Results: Single spot with R_f of 0.677

D. Vapor-Phase Chromatography

Instrument: Hewlett-Packard 7610A

Detector: Flame Ionization at 300°C

Column: A. 10% DC-200 on 80/100 Gas Chrom Q, 4' x 1/4" glass at 125°C

B. 1% x E-60 on 80/100 Gas Chrom Q, 4' x 4" glass at 125°C

Inlet Temperature: 200°C

Results: A. Major peak with a retention time of 5.1 minutes, and a very minor (less than 0.1%) peak at a retention time of 2.5 minutes

B. Single homogeneous peak at a retention time of 2.6 minutes

E. Spectral Data

1. Infrared: Consistent with structure (Figure 5)

2. Nuclear Magnetic Resonance: Consistent with structure (Figure 6)

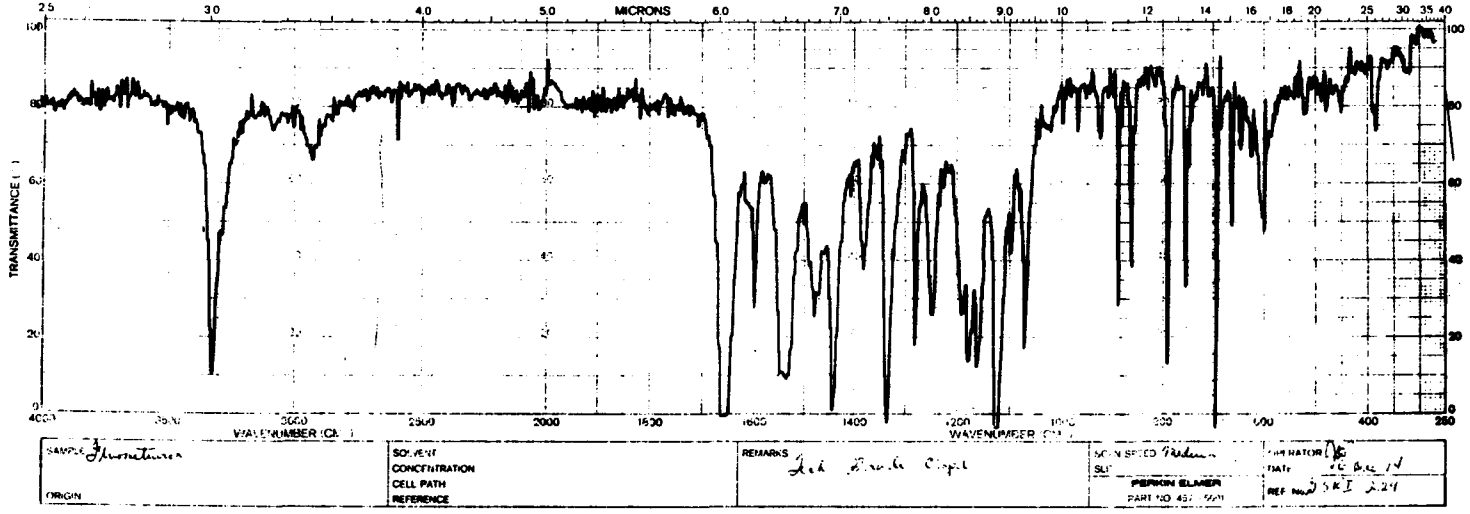


Figure 5. Infrared Absorption Spectrum of Fluometuron, KBr disc (20 mg/300 mg KBr), Batch No. FL-741086

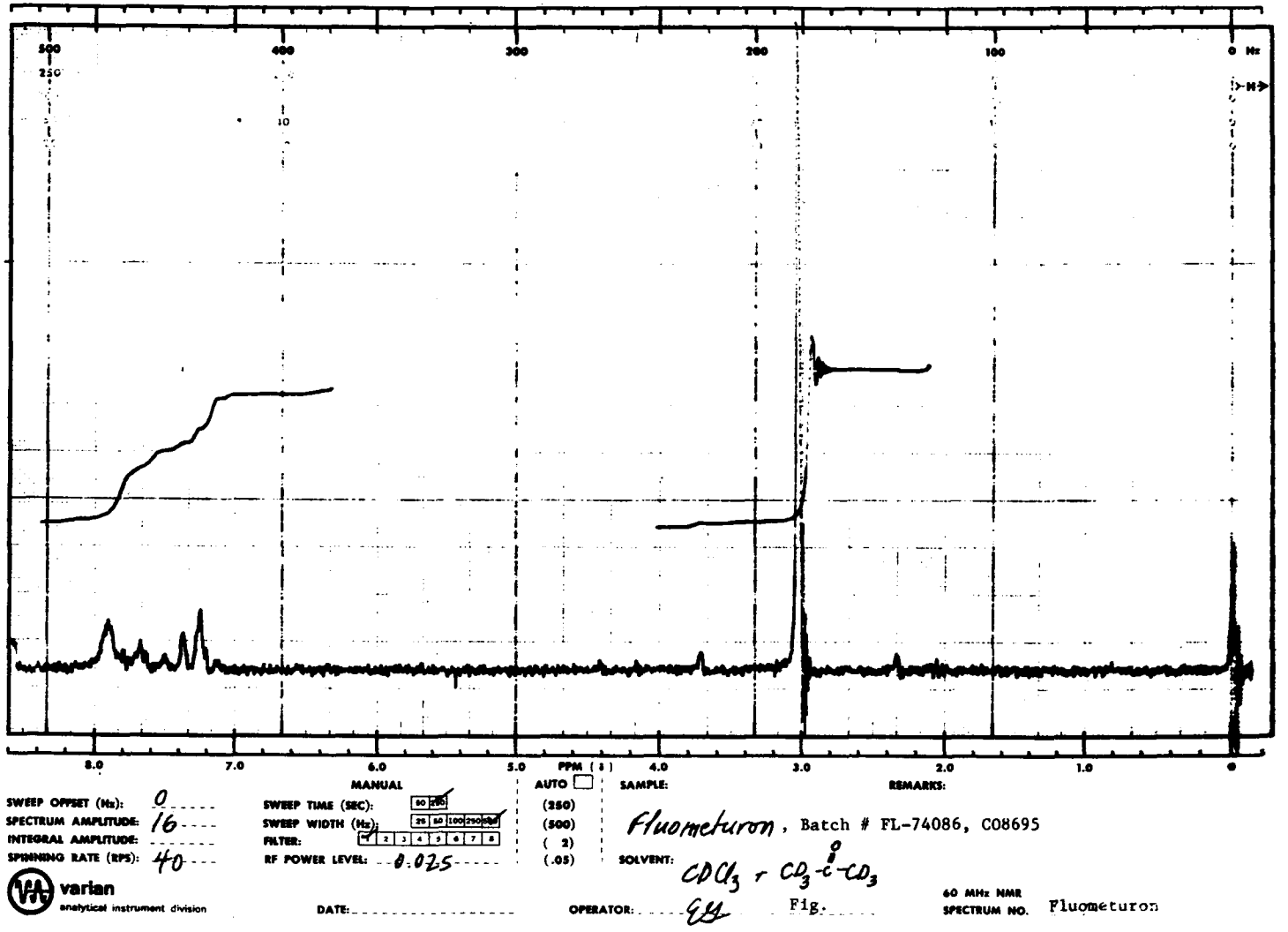


Figure 6. Nuclear Magnetic Resonance of Fluometuron

APPENDIX F

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF FLUOMETURON

Appendix F

Analyses of Formulated Diets for Concentrations of Fluometuron

A 10-g sample of the formulated diet was shaken with 250 ml of benzene at room temperature for 3 hours on a wrist action shaker. The feed was allowed to settle and a 1-ml aliquot of the benzene extract was removed and quantitatively analyzed for fluometuron by vapor-phase chromatography (electron capture detector, 10% DC-200 on Gas Chrom Q column at 120°C). Recoveries were checked with fluometuron-spiked samples carried through the work-up and analysis.

Theoretical Concentration in Diet (ppm)	No. of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
1,000	13	984.0	3.90	905-1,037
500	13	486.8	2.85	457-509
250	13	246.5	6.66	214-273
125	13	123.7	5.09	114-136

Review of the Bioassay of Fluometuron* for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup of the
Clearinghouse on Environmental Carcinogens

February 15, 1980

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Fluometuron for carcinogenicity.

The primary reviewer for the report on the bioassay of fluometuron said that fluometuron was not carcinogenic in rats or female mice and that equivocal results were obtained in treated male mice. Because of this finding and the fact that both the rats and mice may have been able to tolerate higher dosages, the Program staff concluded that additional testing of fluometuron was warranted. The reviewer indicated that the study was typical of the standard NCI bioassay test. Based on the results of the subchronic study, he agreed that the dose levels chosen for the chronic study were probably too low. He recommended that fluometuron be retested because of the questions raised by this study. Based on the results, however, the primary reviewer indicated that it would not appear that fluometuron posed a carcinogenic risk to human beings. He therefore moved that the report be accepted as written and that a retest of fluometuron be considered. The motion was seconded and approved unanimously.

Members present were:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
David B. Clayson, Eppley Institute for Research in Cancer
Joseph Highland, Environmental Defense Fund
William Lijinsky, Federick Cancer Research Center
Henry C. Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Louise Strong, University of Texas Health Sciences Center

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

*U.S. GOVERNMENT PRINTING OFFICE : 1980 0-311-201/3150

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

REPORT ON BIOASSAY OF FLUOMETURON FOR POSSIBLE CARCINOGENICITY

Availability

Fluometuron (CAS 2164-17-2) has been tested for cancer-causing activity with rats and mice in the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute. A report is available to the public.

Summary: A bioassay of the phenylurea herbicide fluometuron for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Under the conditions of this bioassay, fluometuron was not carcinogenic for F344 rats or for female B6C3F1 mice. Equivocal results were obtained for male B6C3F1 mice which may have had an increase incidence of hepatocellular tumors. Because of the equivocal findings and because both rats and mice may have been able to tolerate higher doses, it is concluded that additional testing of fluometuron for carcinogenicity is warranted.

Single copies of the report, Bioassay of Fluometuron for Possible Carcinogenicity (T.R. 195), are available from the Office of Cancer Communications, National Cancer Institute, Building 31, Room 10A21, National Institutes of Health, Bethesda, Maryland 20205.

Dated: September 19, 1980

Director
National Institutes of Health

(Catalogue of Federal Domestic Assistance Program Number 13.393, Cancer Cause and Prevention Research)

NIH Publication No. 80-1751
August 1980